# Dronedarone and Atrial Fibrillation

Abraham M. Karkowsky, M.D., Ph.D.
FDA Cardiovascular and Renal Advisory Committee
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# Reviewers:

- Chemistry- D.R. Lu, Ph.D. and W. Timmer, Ph.D.
- Biopharmaceutics- R. Kumi, Ph.D.
- Pharmacology- E. Hausner, D.V.M.
- Pharmacology Statistics- Jialu Zhang, Ph.D.
- Medical- G. Moreschi, M.D., M.P.H.
- Statistics- V. Freidlin, Ph.D.

# Biopharmaceutic Points to Consider

- Dronedarone demonstrates non-linear kinetics
- Dronedarone is poorly bioavailable (4% fasted; 15% fed). It is a CYP3A4 substrate. Ketoconazole increases $C_{max}$ 9-fold and AUC 15-fold.
- Dronedarone interacts with P-gP and can increase digoxin exposure 2.5-fold.
- Only approximately 10% of plasma radioactivity after orally administered tracer can be accounted for by drug and major metabolite.
- At least 30 metabolites, nearly all unidentified, were isolated after tracer studies. Twenty of these metabolites represent $\geq$ 1% of the administered dose.

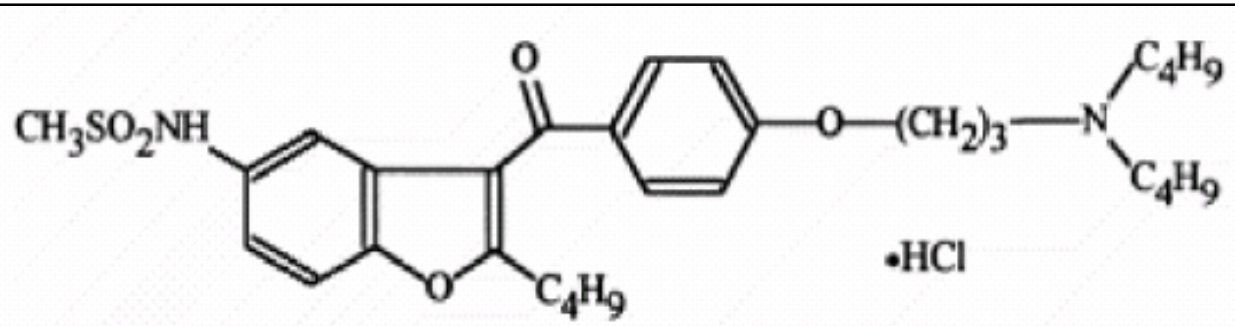
# Toxicology points to consider

- Dronedarone in one in vitro model systems was a mutagen. In other model in vitro or in vivo systems it was not a mutagen.
- The executive carcinogenic advisory committee considered the results of animal carcinogenicity studies to suggest drug-related tumors in the animal models.
- Dronedarone is a teratogen in at least one model species.

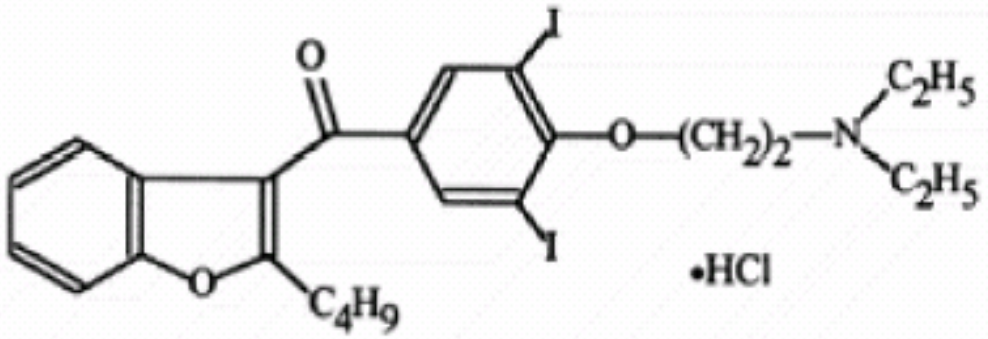
# Points to consider-pharmacology

- Considering the $C_{max}$ of dronedarone and the receptor-binding constants:
  - Dronedarone is potentially a negative inotrope (blocks sodium channels, blocks $\beta_1$-adrenergic sites and alters the generation of adenyl cyclase)
  - Dronedarone would likely prolong cardiac repolarization (blocks potassium channels; e.g., hERG).

# Comparison of the Structure of Dronedarone (SR33589B) and Amiodarone




SR33589B/Dronedarone (MW=593)




Amiodarone (MW=682)

# Dronedarone may not be an analog of amiodarone

- Differences were designed to mitigate toxicity of amiodarone.

but

- The binding of dronedarone and amiodarone ($EC_{50}$) and their in vivo concentrations may not be proportional.
- The activity and concentrations of active metabolites may be entirely different.

# Efficacy studies

# Delay in time to recurrence of atrial fibrillation:

- **DAFNE**- Phase 2 dose-ranging study
- **EURIDIS-** Delay in recurrence
- **ADONIS**- Delay in recurrence

EURIDIS and ADONIS were performed under the same protocol.

# Rate control

- **ERATO**- Holter study of rate control

# Morbidity-Mortality studies

- **ANDROMEDA**- In heart failure patients, not necessarily in Afib/Afl- a safety study. This type of study is standard for an antiarrhythmic drug to establish the safety in a vulnerable (cardiovascular) population.
- **ATHENA-** In patients with history of Afib/Afl. The study was performed to define a population for which dronedarone may be safely used.

# Delay in recurrence and rate control studies

- DAFNE, ADONIS, EURIDIS and ERATO discussed by sponsor.
- Only DAFNE explored a dose range and concluded that the lowest dose, 400 mg BID, which was studied was to be brought into the outcome development programs.

# Morbidity-Mortality studies

# ANDROMEDA-study

- Primary end point: Time to death or hospitalization for worsening heart failure.

- Inclusion: Recently (within 1 month) symptomatic patients hospitalized (or referred to specialty heart failure clinic) for heart failure. Patients were NYHA Class II-IV. May have just been treated with i.v. diuretics and could be ready for discharge. Wall motion index (based on centrally read 2D-echo) $\leq$ 1.2 and one exacerbation of symptoms within last month. Did not have to have atrial fibrillation or could have chronic atrial fibrillation.

- Exclusion: Acute pulmonary edema (within 12 hours), requiring pressors or respirator (within 1 week of enrollment) or had an MI (within 1 week).

# ANDROMEDA Study

- Hospitalizations and deaths were adjudicated by an external committee

- Study discontinued early due an excess of deaths among dronedarone patients.

# ANDROMEDA study events and deaths

| Parameter | Placebo N=317 | Dronedarone N=310 | Hazard ratio (95% CI | Log-rank p-value |
|---|---|---|---|---|
| Death | 12 | 25 | 2.13 (1.1-4.2) | 0.03 |
| Died or hospitalized for worsening heart failure | 40 | 53 | 1.38 (0.92-2.1) | 0.12 |
| Number hospitalized for worsening failure | 31 | 39 | Not calculated | 0.27 |
| Number hospitalized for cardiovascular reasons | 50 | 71 | Not calculated | 0.02 |

# Adjudicated causes of deaths in the ANDROMEDA study

**Adjudicated causes of death are shown below and (fraction of population)-ANDROMEDA**

| | Placebo (N= 317) | Dronedarone (N=310) |
|---|---|---|
| Number of Events | 12 (3.8%) | 25 (8.1%) |
| Cardiovascular death: | 9 (3%) | 24 (8%) |
| MI | 2 (1%) | 0 |
| Worsening CHF | 2 (1%) | 10 (3%) |
| Documented arrhythmia | 2 (1%) | 6 (2%) |
| Procedure related | 0 | 1 (<1%) |
| Other CV reason | 0 | 2 (1%) |
| Presumed CV reason | 3 (1%) | 5 (2%) |
| Non-cardiovascular | 2 (1%) | 1 (< 1%) |
| Cancer | 1 (< 1%) | 1 (< 1%) |
| Other | 1 (<1%) | 0 |
| Non-adjudicated death | 1 (<1%) | 0 |

# NYHA class and the risk of death in the ANDROMEDA study.

- Placebo- NYHA

NYHA II- 5/118 (4.2%)

NYHA III- 7/186 (3.8%)

NYHA IV-0/13 (0%)

- Dronedarone-NYHA

NYHA II-7/126 (5.6%)

NYHA III-17/178 (9.6%)

NYHA IV-1/6 (17%)

# Wall motion index (WMI) at baseline and the risk of death

| Placebo-WMI | Dronedarone-WMI |
|---|---|
| 0.3-0.7= 0/115 (0%) | 0.3-0.7= 9/84 (10.7%) |
| 0.8-0.9= 4/77 (5.2%) | 0.8-0.9= 6/65 (9.2%) |
| 1.0-1.0 =5/67 (7.4%) | 1.0-1.0 =1/75 (1.3%) |
| 1.1-1.2= 3/73 (4.1%) | 1.1-1.2= 9/95 (9.4%) |

- Sponsor's initial hypothesis suggested that mortality was a consequence of early discontinuation of ACE-I or ARB as a result of dronedarone's ability to inhibit creatinine secretion. The discontinuation of ACE-I/ARB directly led to the subsequent mortal or morbid outcomes.
- Note: this hypothesis requires that an asymptomatic serum creatinine increase, provoked the discontinuation of the ACE-I or ARB.

# Deaths do not appear to be related to ACE-I or ARB status during the study

- ANDROMEDA Study and ACE-I or ARB Use

**Outcome of ANDROMEDA based on ACE-I/ARB status**

| | Placebo | Dronedarone |
|---|---|---|
| Number enrolled | 317 | 310 |
| Number not on ACE-I /ARB at baseline (A) | 50 | 36 |
| Number who died (% of A ) | 1 (2%) | 6 (16%) |
| Number on ACE-I/ARB at baseline and throughout study(B) | 255 | 255 |
| Number on B who died (% B) | 10 (4%) | 10 (4%) |
| Number who discontinued from ACE-I/ARB (C) | 12 | 19 |
| Number who died (% C) | 1 (8%) | 9 (47%) |

# None of the Patients who Discontinued ACE-I or ARB had asymptomatic creatinine increases

| **Patient I#** | **Demographic: Age sex NYHA** | **Reason for D/C of ACE-I/ARB** |
|---|---|---|
| 1 | 66 y/o F III | Interstitial nephropathy |
| 2 | 81 y/o F II | Heart failure |
| 3 | 70 y/o M III | Unstable angina admitted for CABG procedure |
| 4 | 87 y/o F III | Worse heart failure |
| 5 | 77 y/o F III | Metastatic disease |
| 6 | 56 y/o M III | Worsening renal function |
| 7 | 82 y/o M II | Worse heart failure and pneumonia |
| 8 | 75 y/o M III | Heart failure |
| 9 | 79 y/o F IV | Worse heart failure |

# Conclusion and Result

- The increased mortality of those treated with dronedarone in the ANDROMEDA study cannot be attributed to an inappropriate discontinuation of ACE-I or ARB.
- The outcome of the ANDROMEDA study resulted in a non-approval recommendation. The Division indicated that approval could be reconsidered if efficacy and safety could be demonstrated in a different and defined population.

# ATHENA study

- Inclusion criteria: Elderly (≥ 75 years old) subjects with history of normal sinus rhythm and episode of AFib/AFl within last 6 months. If not in NSR at baseline there is suppose to be an attempt is to convert after anticoagulation. Originally could be ≥ 70 years or <70 years but have additional risk factors.
- Heart failure exclusion criteria: Unstable hemodynamics e.g., acute pulmonary edema (12 hours), NYHA CHF IV, need for pressors (within 4 weeks).

# Major Amendments

- Amendment # 1- dated 8 March 2006 altered the enrollment criteria to include older subjects. Also included an interim analysis after half events have occurred. This amendment was submitted at the time 11 mortal events were recorded.
- Amendment # 2-dated 25 August 2006 increased sample size to 4300 from 3700 (45 mortal events already occurred) based on blinded evaluation of mortal events.
- Interim analysis performed, captured data through 30 August 2006; 3673 patients were already enrolled. There were 46 mortal events [22 group A and 24 group B] and 693 total endpoints captured; [342 group A and 251 group B]. Steering committee only to be supplied with conclusion.
- Amendment # 3- dated 5 January 2007- Transferred categorization of mortal events to the Steering Committee. Added a symptom assessment (83 mortal events already occurred).

# The SAP was submitted after the interim look

- Statistical analytic plan, dated 5 March 2008, after all subjects completed the study and after the interim look. The secondary endpoints were rearranged at this time. CV hospitalization was placed higher in the hierarchy of secondary endpoints than CV mortality.

# Endpoints

- Primary endpoint
  - Time to first cardiovascular hospitalization or death

- Secondary endpoint: (as a hierarchy)
  - All cause death
  - Cardiovascular hospitalization
  - Cardiovascular death

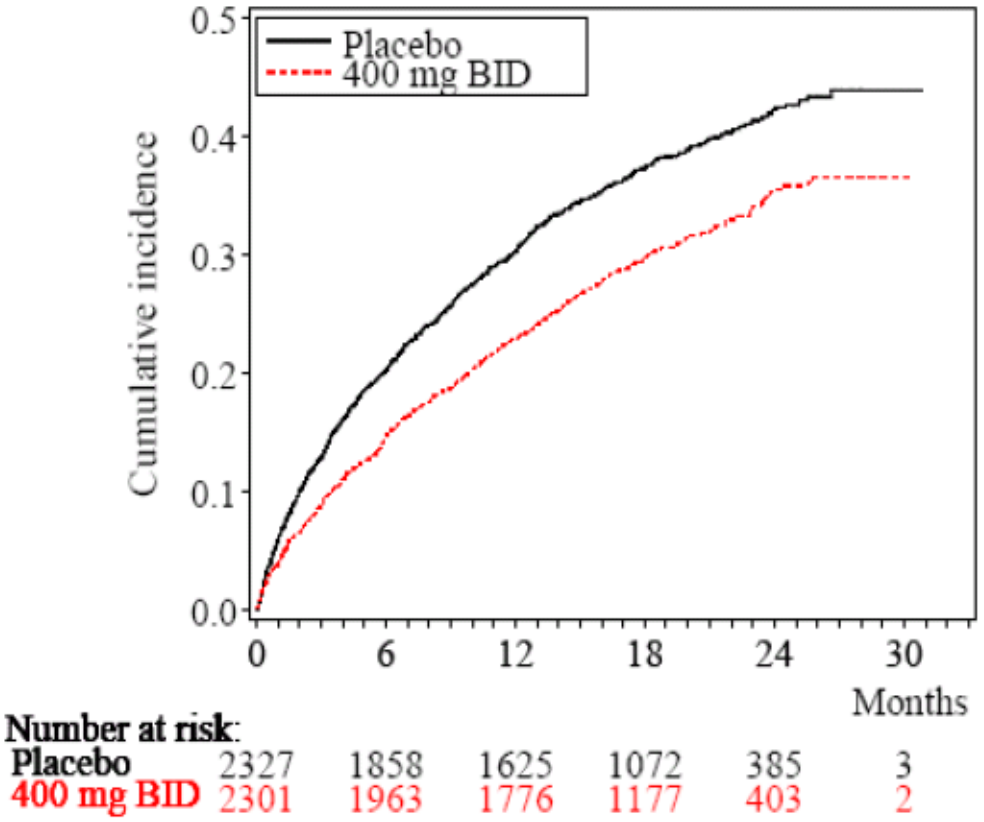
Time of follow-up 1 year after last subject enrolled (date December 30, 2006); follow up period till December 30, 2007.

# Disposition of subjects ATHENA study

**Disposition of subjects in the ATHENA study**

| Placebo | Dronedarone |
|---|---|
| Total Randomized N=4628 | |
| Randomized N= 2327 | Randomized N=2310 |
| Completed study N=2325<br>Lost to follow-up N=2 | Completed study N= 2310<br>Lost to follow-up N= 0 |
| Completed on drug N= 1611<br>Discontinued drug but followed N=716<br>Reason for discontinuation:<br>Adverse event N= 191<br>Poor compliance N= 14<br>Subject's request N=175<br>Other N =336 | Completed on drug N= 1605<br>Discontinued drug but followed N=696<br>Reason for discontinuation:<br>Adverse event N= 293<br>Poor compliance N= 14<br>Subject's request N=173<br>Other N=216 |

# ATHENA Study: Time to First Cardiovascular Hospitalization or Death




- P<<0.001

# All-cause mortality (prior to Dec 30, 2007) was not statistically different comparing dronedarone to placebo

- Placebo: N=135
- Dronedarone: N= 115

- Log rank p-value 0.24

- All-cause Mortality Was Not Significant, Therefore, Additional Analyses are Exploratory in Nature

# First cardiovascular hospitalizations – ATHENA per sponsor

| | Placebo (N=2327) | Dronedarone (N=2301) | HR (95%CI)+ |
|---|---|---|---|
| Any Hospitalization | 859 (37%) | 675 (29%) | 0.75 (0.67, 0.82) |
| Atrial fibrillation and other supraventricular rhythm disorders | 457 (20%) | 296 (13%) | 0.62 (0.53,0.71) |
| Worsening heart failure, including pulmonary edema or dyspnea of cardiac origin | 92 (4%) | 78 (3%) | 0.80 (0.6, 1.09) |
| Myocardial infarction or unstable angina | 61 (3%) | 48 (2%) | 0.74 (0.51, 1.08) |
| Stable angina pectoris or atypical chest pain | 41 (2%) | 45 (2%) | 1.04 (0.69, 1.6) |
| TIA or stroke (except intracranial hemorrhage) | 35 (2%) | 28 (1%) | 0.75 (0.5, 1.5) |
| Transcutaneous coronary, cerebrovascular or peripheral procedure | 31 (1%) | 27 (1%) | 0.82 (0.5, 1.4) |
| Implantation of a pacemaker, ICD or any other device | 29 (1%) | 32 (1%) | 1.04 (0.6, 1.7) |
| Major bleeding (requiring two or more units of blood) or intracranial hemorrhage | 24 (1%) | 21 (1%) | 0.82 (0.45, 1.5) |
| 11 additional categories | 89 (4%) | 100 (4%) | ---------- |

# Summary of first cardiovascular hospitalizations

- Major difference in first hospitalization favored dronedarone.
- Nearly all effect due to atrial fibrillation hospitalizations
- The case report forms did not capture whether subject was hemodynamically unstable, had an exacerbation of heart failure or was admitted for anticoagulation. It is unclear why these patients were hospitalized for atrial fibrillation.

| SR33589B EFC5555 | Country No. | Centre No. | Subject No. | NO | 801 Page | Hosp.number |
|---|---|---|---|---|---|---|
| **VISIT 99** | V 99 | Subject initials | | | | |

Please report only hospitalizations (i.e. admission with an overnight stay in hospital covering at least 2 consecutives dates) which, occur after randomization and that were not scheduled prior to randomization.

## HOSPITALIZATION REPORT C.CLINHOSP_1

**HOSPITALIZATION STATUS:**

- Initial Hospitalization ☐
- Prolonged hospitalization due to a new event ☐
- Date of admission or date of decision to prolong hospitalization: ☐☐☐☐/☐☐/☐☐ (year / month / day)
- Number of nights in ICU/CCU: ☐☐
- In step down unit of medium care: ☐☐
- on ward or on floor: ☐☐
- **HOSPITALIZATION FOR CARDIOVASCULAR REASON?** ..... Yes ☐ No ☐

↳ **IF YES,** specify:

- Main cause for cardiovascular hospitalization *(please refer to the opposite page to report the appropriate code)*: ☐☐
- Does the patient have left CHF? ..... Yes ☐ No ☐

↳ If yes, specify NYHA class: I ☐ II ☐ III ☐ IV ☐

*(please refer to the opposite page of page 8 for NYHA classification)*

↳ **IF NO,** please complete an AE form and a SAE form (with the reason for non cardiovascular hospitalization as description) and forward the 3 forms at the same time.

## HOSPITALIZATION REPORT C.CLINOHSP_1

01. Atherosclerosis related (if not otherwise specified)
02. Myocardial infarction or unstable angina
03. Stable angina pectoris or atypical chest pain
04. Syncope
05. TIA or Stroke (except intracranial hemorrhage)
06. Atrial Fibrillation and other supraventricular rhythm disorders
07. Non-fatal cardiac arrest
08. Ventricular Arrhythmia
09. Cardiovascular surgery except cardiac transplantation
10. Cardiac Transplantation
11. Implantation of a pacemaker, ICD or any other cardiac device
12. Transcutaneous coronary, cerebrovascular or peripheral procedure
13. Blood pressure related (hypotension, hypertension; except syncope)
14. Cardiovascular infection
15. Major Bleeding (requiring two or more units of blood or any intracranial hemorrhage)
16. Pulmonary Embolism or deep vein thrombosis
17. Worsening CHF, including pulmonary edema or dyspnea of cardiac origin

# Categorization of mortal events

- Data collected by investigator through case report forms. Information captured was minimal.
- Event originally categorized by investigator
- Steering Committee re-categorized events as:
  - Cardiac/arrhythmic
  - Cardiac/non-arrhythmic
  - Vascular/non-cardiac
  - Non-vascular
- Committee consisted of 5 independent cardiologists and 3 sponsor's members. Only cardiologists were involved in categorization. Categorization occurred after the interim look. The Steering Committee was to be blinded as to the results other than to discontinue or continue the study.

- The cardiovascular mortality rates up to Dec 30, 2007 in ATHENA were as assessed by the Steering Committee's categorization:
- Placebo = N=91
- Dronedarone N=65

- Nominal log-rank p-value 0.037

Do cause-specific measurements clarify or allow for a second statistical look?

# Criteria for Cardiovascular or Non-cardiovascular Classification-ATHENA

- Cardiovascular
  - Aortic dissection
  - CHF
  - Death during cardiovascular intervention (includes PCI and surgery)
  - Hemorrhage
  - Myocardial infarction
  - Unstable angina
  - Pulmonary peripheral embolism
  - Sudden death
  - Ventricular fibrillation
  - Unknown cause
- Non-cardiovascular
  - Sepsis
  - Neoplasms
  - Asthenia
  - Chronic obstructive pulmonary disease
  - Hepatitis
  - Influenza
  - Interstitial lung disease
  - Multi-organ failure
  - Edema
  - Pneumonia
  - Pulmonary fibrosis
  - Dementia
  - Trauma (drowning , electrocution, crime, brain contusion
  - Renal failure
  - Failure to thrive
  - Death

# Comments on the classification of events

- Case report forms only capture small amount of data.
- The initial assessment by the on-site investigator had ECG and renal data that could unmask treatment (e.g., QT prolongation, creatinine increases and GI symptoms).
- Consistency (see example below).
- Categories of cardiovascular and non-cardiovascular not appropriate for antiarrhythmic drug trial.
- Only a few events (N=2 to 5) with re-categorization removes nominal effect.
- Errors in classification add a different form of uncertainty. All-cause mortality includes events not likely to be altered by the use of an antiarrhythmic drug .

Subject number 246008008 (Treated with dronedarone –**classified as a brain contusion and was not considered cardiovascular event**).

This patient treated with low dose of aspirin and oral anticoagulant (international normalized ratio at 1.1), fell from his bicycle and became unconscious with profuse bleeding from nasopharynx, on Day 362. Skull fracture and large right subdural hematoma, massive edema of the brain with transtentorial and subfalcine herniation were observed on computed tomography scan. Furthermore he suffered from 3 rib fractures without pneumothorax. Despite poor prognosis, an emergency evacuation of subdural hematoma was performed. During this procedure the patient experienced an uncontrollable intracranial pressure increase leading to cerebral edema and the patient died the same day. No autopsy was performed.

Patient 528003011 treated with placebo (was **treated as a cardiovascular event**).

This patient, who was taking oral anticoagulants, was admitted to a Turkish hospital on Day 158 after falling and hitting his head during a visit to Turkey. The patient went into a coma due to subarachnoid and intracerebral bleeding, which was treated by a surgical decompensation (sic). The investigational product was discontinued. On Day 169 the patient was transported back to the Netherland with a Glasgow coma scale of 6. Due to the poor (infaust)(sic) neurological prognosis, it was decided that neither resuscitation nor readmittance to the intensive care unit should be done in the future. The patient died in the hospital as a consequence of the initial event on Day 201.

# Summary regarding cardiovascular mortality

- Cardiovascular mortality only an exploratory analysis
- Potential errors in the characterization of events
- Results inconsistent with results of ANDROMEDA study which demonstrated an increase in CV mortality- Gradient of poor outcome relative to heart failure status hard to reconcile.

# Summary

- ATHENA was successful in demonstrating a decrease in time to first CV hospitalization or death.
- Overall mortality, the first secondary endpoint- was not different comparing placebo to dronedarone.
  - CV hospitalizations as an exploratory analysis suggest that the benefit was due to atrial fibrillation hospitalizations.
  - CV deaths as an exploratory analysis was suggestive of a benefit in the ATHENA population.

# Safety

# Exposure and Serious Safety ADONIS, EURIDIS, ERATO and DAFNE

| | Placebo | Dronedarone | | |
|---|---|---|---|---|
| | | 400 mg BID | 600 mg BID | 800 mg BID |
| N= | 564 | 989 | 66 | 62 |
| Mean days ± SD | 205 ± 141 | 240 ± 142 | 64 ± 76 | 57 ± 71 |
| Patient-years | 316.7 | 650.3 | 11.6 | 9.7 |
| Serious TEAE (per patient year) | 79 (0.25) | 133 (0.20) | 4 (0.34) | 8 (0.82) |
| Deaths* (per patient year) | 3 (0.009) | 9 (0.014) | 0 | 0 |
| Patients discontinued (per patient year) | 34 (0.10) | 96 (0.15) | 4 (0.34) | 14 (1.4) |
| | | | | |
| * Deaths from first dose till ten days after last dose. | | | | |

Table (2.7.4.2.1.3.1)

# Summary of All Deaths

| | Placebo | Dronedarone |
|---|---|---|
| DAFNE, ERATO, ADONIS, EURIDIS | | |
| Number (events/patient year) | 3 (0.009) | 9 (0.014) |
| ANDROMEDA | | |
| Overall<br>Adjudicated as cardiovascular | 12 (3.7%)<br>9 (2.8%) | 25 (8.1%)<br>24 (7.7%) |
| ATHENA | | |
| Overall<br>Categorized as cardiovascular | 135 (5.8%)<br>91 (3.9%) | 115 (5.0%)<br>65 (2.8%) |

# Summary of Heart Failure Deaths

| | Placebo | Dronedarone |
|---|---|---|
| ANDROMEDA | | |
| Adjudicated as death due to worse heart failure | 2 (1%) | 10 (3%) |
| ATHENA | | |
| Categorized as death due to worse heart failure | 8 (0.3%) | 13 (0.6%) |

# Adverse events in ATHENA > 2%

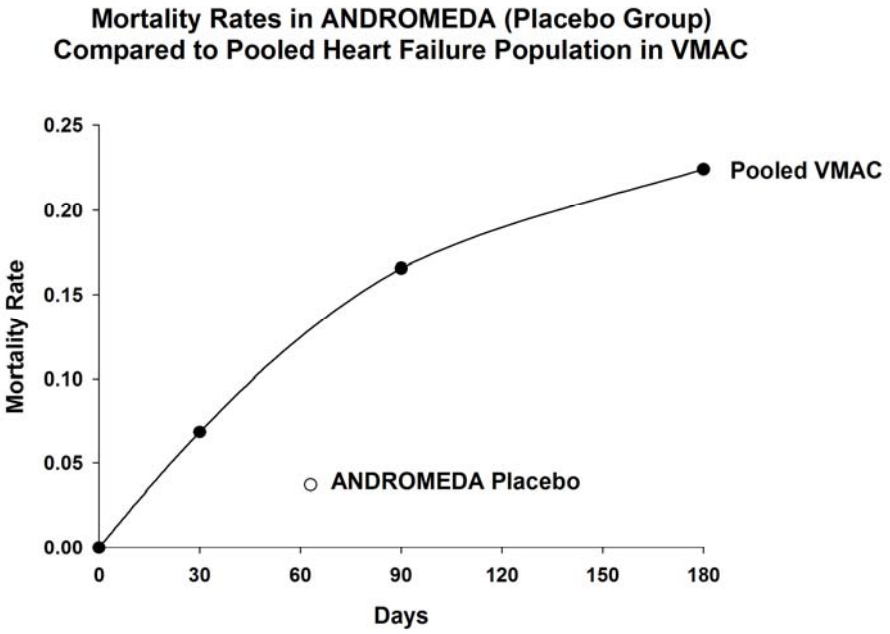
**Adverse events in the ATHENA study (≥2% events in any treatment)**

| | Placebo | Dronedarone |
|---|---|---|
| **Any event** | **1603 (69%)** | **1649 (72%)** |
| **Gastrointestinal disorders** | **508 (22%)** | **600 (26%)** |
| **Diarrhea** | **144 (6%)** | **223 (10%)** |
| **Nausea** | **72 (3%)** | **122 (5%)** |
| **Vomiting** | **27 (1 %)** | **49 (2 %)** |
| **General disorders and administrative site conditions** | **356 (15%)** | **403 (18%)** |
| **Edema peripheral** | **119 (5%)** | **147 (6%)** |
| **Fatigue** | **90 (4%)** | **115 (5%)** |
| **Asthenia** | **47 (2%)** | **68 (3%)** |
| Chest pain | 55(2%) | 52(2%) |
| Respiratory, thoracic and mediastinal disorders | 337 (15%) | 332 (15%) |
| **Dyspnea** | **97 (4%)** | **120 (5%)** |
| Cough | 83 (4%) | 83 (4%) |
| **Investigations** | 206 (9%) | 309 (13%) |
| **Blood creatinine increased** | 31 (1%) | 108 (5%) |
| INR increased | 47 (2%) | 48 (2%) |
| **Cardiac disorders** | **221 (10%)** | **260 (11%)** |
| **Bradycardia** | **28 (1%)** | **81 (4%)** |
| **Skin and subcutaneous tissue disorders** | **176 (7%)** | **237 (10%)** |
| **Rash** | **37 (2%)** | **60 (3%)** |

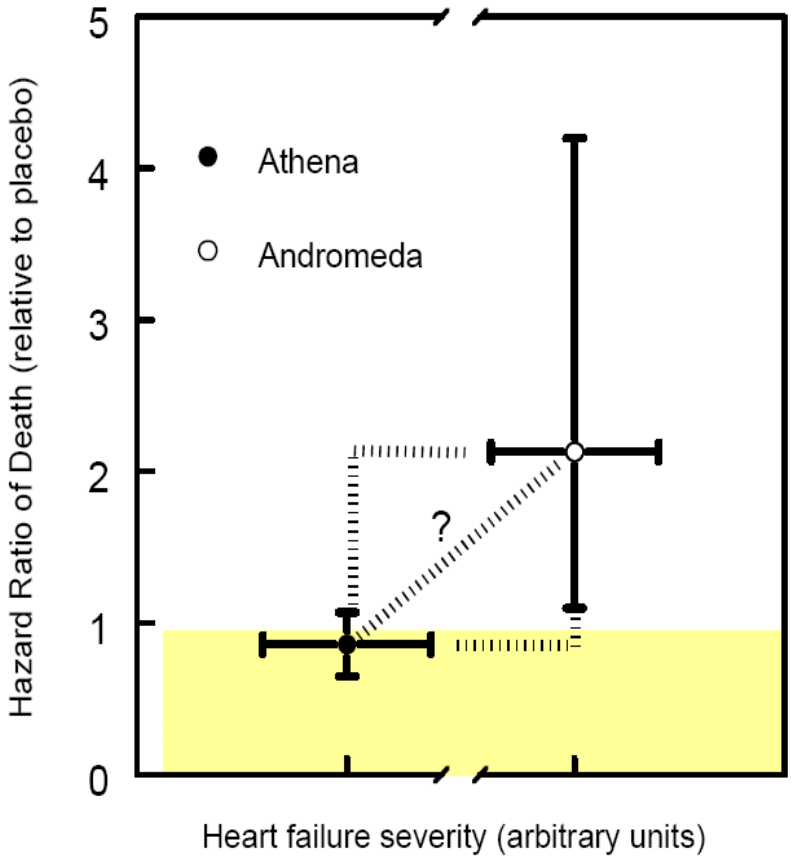
# Comparison of population in ANDROMEDA and ATHENA- it would have been unethical to perform ATHENA if the two populations overlapped.

- Andromeda:
  - Population recently hospitalized or clinic visit for heart failure requiring at the minimum iv diuretics.
  - Age- 70; M =76%
  - Median wall motion index =0.9;
  - EF?
  - NYHA None/I/II/III/IV= 0%/0%/39%/58%/3%
- Athena:
  - Elderly population with history of Afib/Afl and normal NSR
  - Age- 72; M=55%
  - Median wall motion index?
  - Mean EF= 57%
  - NYHA None/I/II/III/IV= 70%/8%/17%/5%/0%

# How sick was the ANDROMEDA population?



# So, where is the cross-over benefit/harm point?



# Dronedarone and heart failure

- There are two studies which remarkably different outcomes. Both studies contribute data points to risk based on heart failure status.
- If not for the results of the ANDROMEDA study, subgroup analyses would offer comfort.
- In the presence of the ANDROMEDA results, there has to be an inflection point to negative mortal outcomes based on degree of heart failure.
- Small numbers in the tails of the population or in subgroups of populations make the conclusions less reliable, both for risk and for comfort.

# Conclusion

- The results of ADONIS, EURIDIS and ATHENA suggest a benefit in delay of recurrence of AFib.
- ANDROMEDA study suggests subjects with heart failure have an adverse outcome.
- ATHENA study suggests no overall adverse mortality outcome in patients without severe heart failure and a decrease in Afib hospitalizations.
- Where is the cross-over point?

END